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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/567,266	05/29/2008	Wolfram Eichner	14503-005US1 F62339PCUS H	4435

26191 7590 11/15/2011

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EXAMINER	
GOON, SCARLETT Y	
ART UNIT	**PAPER NUMBER**
1623	

NOTIFICATION DATE	DELIVERY MODE
11/15/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/567,266	EICHNER ET AL.	
	Examiner	Art Unit	
	SCARLETT GOON	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 September 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-3,5-8,10,13,54-56,72,73 and 75-78* is/are pending in the application.

5a) Of the above claim(s) *1-3,5-8,10,13,54,55,77 and 78* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *56,72,73,75 and 76* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *21 September 2011*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to Applicants' Remarks filed on 21 September 2011. No amendment to the claims was submitted.

Claims 1-3, 5-8, 10, 13, 54-56, 72, 73 and 75-78 are pending in the instant application.

Claims 1-3, 5-8, 10, 13, 54, 55, 77 and 78 were previously withdrawn from further consideration in the Office Action dated 21 March 2011 pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and/or nonelected species, there being no allowable generic or linking claim.

Claims 56, 72, 73, 75 and 76 will be examined on the merits herein.

Priority

This application is a National Stage entry of PCT/EP2004/008818 filed on 6 August 2004 and claims priority to EPO foreign application 04005874.5 filed on 11 March 2004, PCT/EP03/08858 filed on 8 August 2003, PCT/EP03/08829 filed on 8 August 2003, and PCT/EP03/08859 filed on 8 August 2003, and U.S. provisional application no. 60/552,281 filed on 11 March 2004. A certified copy of the foreign priority documents in English has been received.

Information Disclosure Statement

The information disclosure statement (IDS) dated 21 September 2011 comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609, except where noted.

Accordingly, it has been placed in the application file and the information therein has been considered as to the merits.

Foreign patent document desig. ID 79 was not considered because the full reference was not provided to the Office. Portions of the document were submitted in separate files, some of which were duplicates.

Other documents desig. ID 91 was not considered because a copy of the reference was not submitted to the Office.

Other documents desig. ID 97 was not considered because a translation of the foreign document was not submitted to the Office.

Other documents desig. ID 118 was not considered because only the first page of the reference was submitted to the Office.

Other documents desig. ID 127 and 131 were amended to correct for the cited editor and page number, respectively.

The following rejections of record in the previous Office Action are maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 56, 72, 73, 75 and 76 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0605963 A2 to Wright (IDS dated 26 December 2006), in view of U.S. Patent No. 5,824,778 to Ishikawa *et al.* (hereinafter referred to as the '778 patent; of record), in view of journal article publication by Rotondaro *et al.* (of record), in view of U.S. Patent No. 6,083,909 to Sommermeyer *et al.* (hereinafter referred to as the '909 patent; IDS dated 26 December 2006), in view of journal article publication by Peluso *et al.* (of record), in view of WIPO publication WO 80/02374 by Berger *et al.* (IDS dated 14 October 2009).

Wright teaches methods and compounds for modifying polypeptides with PEG or other water-soluble organic polymers. Protein and other similar organic molecules are chemically modified by covalent conjugation to water-soluble organic polymers, such as PEG, because of the desirable properties conferred on the polypeptides by attachment of the water-soluble polymers. The desirable properties include solubility in aqueous solutions, increased stability during storage, reduced immunogenicity, increased resistance to enzymatic degradation, compatibility with a wider variety of drug administration systems, and increased *in vivo* half-life (p. 2, lines 11-16). Conjugation of mPEG to a cysteine residue of EPO is known (p. 3, lines 5-9). However, Wright teaches that it may be advantageous to couple water-soluble reagents to the carbohydrate moiety of a glycoprotein rather than to the polypeptide backbone amino acids because of differences in charge displacement, steric hinderance, amino acid residues at active sites, and other problems that may disrupt the structure and function of the polypeptide component of the water-soluble polymer modified glycoproteins (p. 3, lines 38-46). By providing for water-soluble polymer reagents that may be coupled to the carbohydrate moiety of glycoproteins it may be possible to covalently conjugate water-soluble polymers to proteins without substantially adversely affecting the biological activity of proteins that would be adversely affected through coupling at other amino acid residues (p. 3, lines 47-50). Wright teaches that hydrazine and oxylamine derivatives of water-soluble polymers, such as PEG, may be covalently attached to proteins through reactions with aldehyde groups or other suitable functional groups present on the protein of interest (p. 7, lines 5-11). Aldehyde groups may be introduced

by partially oxidizing the hydroxyl groups on the polypeptide, such as hydroxyl groups present on the carbohydrate moieties of the polypeptide, with galactose oxidase or periodate (p. 7, lines 11-16). Hydrazide and oxylamine derivatives are further disclosed (p. 7, lines 19-58). More specifically, Formula (VI) discloses a dihydrazide linker. Examples of PEG water soluble polymers include dextran and dextran derivatives, cellulose and cellulose derivatives, starch and dextrines, polyethylene glycol and derivatives thereof, heparin and fragments of heparin, polyvinyl alcohol and polyvinyl ethyl ethers, polyvinylpyrrolidone, α,β-poly[2-hydroxyethyl)-DL-aspartamide, and polyoxyethylated polyols. (p. 7, line 58 – p. 8, line 5). Wright further teaches that the disclosed preparation may be administered alone or in an admixture with a pharmaceutical carrier or diluent selected with regard to the intended route of administration and standard pharmaceutical practice (p. 12, lines 14-21). Polypeptides of interest for water-soluble polymer derivatization include hormones, lymphokines, cytokines, growth factors, enzymes, vaccine antigens, and antibodies (p. 4, lines 26-29). Methods for the synthesis of mPEG-hydrazide from mPEG-OH (p. 12, line 55 - p. 13, line 37) and mPEG-semicarbazide from mPEG-NH_2 (p. 13, line 50 – p. 14, line 16) are further disclosed. Methods for the modification of a peptide with mPEG-hydrazide and mPEG-semicarbazide are further exemplified with EPO wherein EPO is oxidized with sodium periodate followed by conjugation of the resulting aldehyde with PEG (p. 18, line 26 - p. 19, line 14).

The teachings of Wright differ from that of the instantly claimed invention in that Wright does not expressly teach conjugation of a water soluble polymer to a polypeptide

via a hydrazone or oxime linkage wherein the polypeptide is G-CSF, nor does Wright teach conjugation of G-CSF to a polymer that is HES.

The Ishikawa '778 patent discloses a polyethylene glycol-modified human granulocyte colony stimulating factor (G-CSF). The polyethylene glycol (PEG) is covalently bound through amino acid residues of the polypeptide of human G-CSF, such as those having a free amino group (e.g. lysine and the N-terminal amino acid residue) and those having the free carboxyl group (e.g. aspartic acid, glutamic acid and the C-terminal amino acid residue) (column 2, line 66 – column 3, line 8). The PEG modified human G-CSF has a more enduring pharmacological effect, which may be possibly attributed to its prolonged half-life in the body (column 4, lines 16-18). The PEG modified human G-CSF has essentially the same biological activity as an intact human G-CSF and is therefore useful in the treatment of general haematopoietic disorders, including those arising from chemotherapy or from radiation therapy (column 4, lines 22-31). The PEG modified human G-CSF may be formulated into pharmaceuticals containing also a pharmaceutically acceptable diluent, an agent for preparing an isotonic solution, a pH-conditioner, and the like, in order to administer them into a patient (column 4, lines 32-36). The pharmaceuticals may be administered subcutaneously, intramuscularly, intravenously, or orally, depending on a purpose of treatment. A dose may be also based on the kind and condition of the disorder of a patient to be treated, being normally between 0.1 μg and 5 mg by injection and between 0.1 mg and 5 g in an oral administration to an adult (column 4, lines 37-43).

Rotondaro *et al.* disclose the purification and characterization of two recombinant human granulocyte colony-stimulating factor glycoforms expressed from an engineered CHO cell line (abstract). The glycoforms are attached to the peptide at Thr-133 (p. 117, abstract, paragraph 1). One O-linked glycan has the structure Neu5Ac(α2-3)Gal(β1-3)GalNAc and the other O-linked glycan has the structure Gal(β1-3)[Neu5Ac(α2-3)Gal(β1-3)]GalNAc (p. 117, abstract, paragraph 1).

The Sommermeyer '909 patent teaches haemoglobin-hydroxyethyl starch conjugates, and processes for their preparation. Haemoglobin and hydroxyethyl starch are linked to one another selectively via amide bonds between free amino groups of the haemoglobin and the reducing end group of the hydroxyethyl starch, which is present in oxidized form (column 3, lines 40-45). To prepare the conjugate, preferably hydroxyethyl starch which has an average molecular weight of 1 to 40 kDa is used, hydroxyethyl starch having an average molecular weight of 5 to 20 kDa being particularly preferred (column 5, lines 1-6). The reducing end groups of the hydroxyethyl starch are oxidized and the haemoglobin is bonded to the oxidized end groups of hydroxyethyl starch in a second step (column 5, line 63 – column 6, line 9). An advantage of the conjugate is that it can be administered in high concentrations simultaneously, without the colloidal osmotic pressure being increased as a result (column 4, lines 9-13).

Peluso *et al.* teach chemoselective ligation for the assembly of N-linked glycopeptides mimetics. Chemoselective ligation is an attractive strategy as it allows the convergent synthesis of neoglycopeptides without the need for protecting groups or

activating agents. To illustrate the facileness of the method, Peluso *et al.* developed alanine-β-hydroxylamine (1) and alanine-β-hydrazide (2) as asparagine surrogates for the assembly of N-glycopeptide mimetics (p. 2086, first column, first full paragraph). Conjugation of compounds (1) and (2) with GlcNAc according to chemoselective ligation protocols afforded the desired corresponding products, as shown in Figure 1 (p. 2086, column 2, last paragraph).

Berger *et al.* teach a composition for the controlled release administration of a biologically active compound, comprising a combination of the biologically active compound and hydroxyalkyl starch. Hydroxyalkyl starch, preferably hydroxyethyl starch, is the choice of polymeric drug carrier because this polymer has the property of a low long term *in vivo* persistence, and can also be metabolized, with little, if any, toxicity, or excreted from the body, after it has served its function (p. 3, lines 20-35). Biologically active components can be combined with the polymer directly or through suitable derivatives by chemical bonds (p. 5, lines 21-24). The derivatizing agents are carefully selected so that the drug or an active drug derivative will be released *in vivo*, or the activity of the drug will be maintained while it is bound to the polymer (p. 6, lines 14-17). Derivatizing agents useful for producing the compositions include substantially any non-toxic compound which will link the active compound to the polymer. Polyfunctional organic compounds are useful for this purpose (p. 6, lines 28-31). Hydroxyalkyl starch derivatives can be reacted with proteins, peptides, and amino acids (p. 7, lines 9-11).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Wright *et al.*, concerning methods and

compounds for modifying polypeptides with PEG or other water-soluble organic polymers, with the teachings of the Ishikawa '778 patent, regarding a polyethylene glycol-modified human granulocyte colony stimulating factor, with the teachings of Rotondaro *et al.*, regarding the purification of glycosylated rhG-CSF from an engineered CHO cell line, with the teachings of the Sommermeyer '909 patent, regarding haemoglobin-hydroxyethyl starch conjugates via conjugation at the oxidized reducing end of starch, with the teachings of Peluso *et al.*, regarding chemoselective ligation of N-linked glycopeptides, with the teachings of Berger *et al.*, regarding a composition comprising a combination of a biologically active compound and hydroxyalkyl starch. Since the Ishikawa '778 patent teaches that one of ordinary skill in the art would have been motivated to modify G-CSF with PEG for a more enduring pharmacological effect, one of ordinary skill in the art would have been motivated to combine the teachings and use the method disclosed by Wright *et al.* for the preparation of a PEG-modified G-CSF peptide, in order to receive the expected benefit, as suggested by Wright *et al.*, that it may be advantageous to couple water-soluble polymers to the carbohydrate moiety of a glycoprotein rather than to the polypeptide backbone amino acids because of differences in charge displacement, steric hinderance, amino acid residues at active sites, and other problems that may disrupt the structure and function of the polypeptide component of the water-soluble polymer modified glycoproteins. Since G-CSF is known to be glycosylated, as disclosed in the teachings of Rotondaro *et al.*, one of ordinary skill in the art would have a reasonable expectation of success in using the methods of Wright *et al.* to conjugate PEG, or starch, to G-CSF. Furthermore, in view of the

teachings of Wright *et al.*, it would have been *prima facie* obvious to substitute the PEG water-soluble polymer with starch as Wright *et al.* teach that both PEG and starch, in addition to other water-soluble polymers, are suitable for conjugation to a polypeptide to effect desirable properties conferred on the polypeptides by attachment of the water-soluble polymers, such as solubility in aqueous solutions, increased stability during storage, reduced immunogenicity, increased resistance to enzymatic degradation, compatibility with a wider variety of drug administration systems, and increased *in vivo* half-life.

Although Wright *et al.* teach that starch and their derivatives can be used as suitable water-soluble polymers for conjugation to polypeptides, Wright *et al.* do not expressly teach at what position on starch the conjugation of the polypeptide via hydrazine and hydroxylamine linkers should occur. However, it is known from the prior art that polypeptides can be conjugated to the reducing end sugar of starch, such as in the Sommermeyer '909 patent, which teaches conjugation of hemoglobin to hydroxyethyl starch at its oxidized reducing end. Therefore, in view of the combined teachings of the prior art, it would have been *prima facie* obvious for one of ordinary skill in the art to conjugate the polypeptide, via a linker, to the reducing end of starch since the Sommermeyer '909 patent teaches the reducing end of starch as a feasible site for attachment of hemoglobin. Thus, one of ordinary skill in the art would have a reasonable expectation of success in conjugating a polypeptide to the reducing end sugar of starch. Furthermore, Peluso *et al.* teach that hydrazides can be chemoselectively ligated to a reducing end carbohydrate residue. Since Wright *et al.*

teach conjugation of polypeptides to water soluble polymers via a hydrazine or oxylamine linker, one of ordinary skill in the art would have been motivated to further modify the conjugation method of the Sommermeyer '909 patent by conjugating the polypeptide to starch, via a linker, at the non-oxidized reducing end, in order to receive the expected benefit, as taught by Peluso *et al.*, that chemoselective ligation of an oxime or hydrazide to the reducing end sugar residue is advantageous as it allows convergent synthesis without the need for protecting groups or activating agents. Moreover, while it is noted that the Sommermeyer '909 patent teaches the use of hydroxyethyl starch as the starch, thereby prompting one of ordinary skill in the art to use hydroxyethyl starch, one of ordinary skill in the art would have been further motivated to use hydroxyethyl starch as the starch water-soluble polymer in order to receive the expected benefit, as taught by Berger *et al.*, that hydroxyethyl starch is the choice of polymeric drug carrier because this polymer has the property of a low long term *in vivo* persistence, and can also be metabolized, with little, if any, toxicity, and excreted from the body, after it has served its function.

Since Wright *et al.* disclose various hydrazine derivative linkers, including a carbonic acid dihydrazide linker of formula (VI), and in view of the combined teachings of the prior art, one of ordinary skill in the art would have a reasonable expectation of success in conjugating one end of the dihydrazide linker to the non-oxidized reducing end of starch via chemoselective ligation, such as disclosed by Peluso *et al.*, and further conjugating the other hydrazide end to the oxidized sugar residue of G-CSF.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Response to Arguments

Applicants' arguments, filed 21 September 2011, with respect to the rejection of claims 56, 72, 73, 75 and 76 made under 35 USC § 103(a) as being unpatentable over EP 0605963 A2 to Wright, in view of U.S. Patent No. 5,824,778 to Ishikawa *et al.*, in view of journal article publication by Rotondaro *et al.*, in view of U.S. Patent No. 6,083,909 to Sommermeyer *et al.*, in view of journal article publication by Peluso *et al.*, in view of WIPO publication WO 80/02374 by Berger *et al.*, have been fully considered but they are not persuasive.

Applicants argue that the Examiner has not identified any particular lead compound, nor identified a problem to be solved based on the molecules disclosed in the cited references. Additionally, Applicants argue that importantly, the Examiner has not identified a reason to make the specific molecular modifications required to alter any lead compound in the cited references to result in the conjugates specifically claimed in the present application. More particularly, Applicants argue that the Examiner failed to identify a reason for modifying the prior art universe of polymer-protein conjugates to the presently recited conjugates in which HAS is coupled to G-CSF via a bifunctional carbohydrazide linker, where the linker is selectively coupled to the non-oxidized reducing end of the HAS and to a carbonyl group of G-CSF, such that the conjugate has the instantly claimed structure. Applicants also argue that the Examiner has not set

forth any rationale why modified versions of any of the conjugates described in the cited references would represent identified, predictable solutions to any identified problem of a lead molecule disclosed therein.

Applicants' arguments have been carefully considered but are not persuasive. Although Applicants argued that a particular lead compound has not been identified in the rejection, and has not identified the problem to be solved based on the molecules disclosed in the cited references, Wright teaches the conjugation of water-soluble polymers to proteins via a carbohydrazide linker and expressly teaches conjugation of a PEG-carbohydrazide moiety to the glycoprotein via the carbohydrate moiety of a glycoprotein rather than to the polypeptide backbone amino acids because of differences in charge displacement, steric hinderance, amino acid residues at active sites, and other problems that may disrupt the structure and function of the polypeptide component of the water-soluble polymer modified glycoproteins. Although Wright exemplifies PEG as the water-soluble, Wright expressly teaches that there are other suitable water-soluble polymers, including starch. With regards to the protein, although Wright exemplifies EPO as the glycoprotein, Wright expressly teaches that other polypeptides of interest include growth factors and cytokines. Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *In re Susi*, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493

U.S. 975 (1989). Therefore, in summary, the disclosure of Wright teaches and/or suggests to one of ordinary skill in the art that starch and PEG are each suitable as a water-soluble polymer for conjugation to polypeptides, such as cytokines, hormones and growth factors, via a carbohydrazide linker, wherein the linker is conjugated to the polypeptide via the carbohydrate moiety present on the glycoprotein, further exemplifying PEG conjugated to the oxidized glycan moiety of EPO via a carbohydrazide linker. The Ishikawa '778 patent discloses PEG-modified hG-CSF wherein the PEG moiety is conjugated to a free amino acid on the polypeptide backbone. PEG-modified hG-CSF has a more enduring pharmacological effect compared to the unmodified peptide. Following the guidelines for establishing that a chemical compound is obvious over a compound in the prior art, as clarified by the Federal Circuit in *Takeda Chemical Industries, ltd. v. Alphapharm Pty., Ltd.*, and cited by Applicants, either the starch-carbohydrazide linker-glycoprotein conjugate of Wright, or the PEG-hG-CSF conjugate of the Ishikawa '778 patent, can be considered to be a lead compound for further modification. If one were to consider the starch-carbohydrazide linker-glycoprotein conjugate of Wright to be the lead compound, one of ordinary skill in the art would have been motivated to specifically use hG-CSF as the glycoprotein in the conjugate, or substitute EPO in the exemplified conjugate with hG-CSF, as the Ishikawa '778 patent teaches that PEG-modified hG-CSF has a more enduring pharmacological effect, thereby providing one of ordinary skill in the art the motivation for narrowing the prior art universe of proteins to a finite number of identified, predictable solutions in the prior art. The reason for making the specific molecular

modifications is found in Wright, which teaches that conjugation of a PEG-carbohydrazide moiety to the glycoprotein via the carbohydrate moiety of a glycoprotein rather than to the polypeptide backbone amino acids is advantageous because of differences in charge displacement, steric hinderance, amino acid residues at active sites, and other problems that may disrupt the structure and function of the polypeptide component of the water-soluble polymer modified glycoproteins if the conjugate occurs on the amino acid of the polypeptide backbone. Since Rotondaro *et al.* teach that hG-CSF is a glycoprotein containing O-linked glycans that terminate in a sialic acid or galactose residues, both of which can be oxidized to contain a carbonyl group via the chemical or enzymatic methods disclosed in Wright, one of ordinary skill in the art would have a reasonable expectation of success in oxidizing the terminal galactose residue of hG-CSF using methods disclosed in Wright, and further conjugate the water-soluble linked hydrazide moiety to the oxidized galactose moiety of hG-CSF to yield a conjugate in which the water-soluble moiety, such as starch, is conjugated to hG-CSF via a carbohydrazide linker, wherein the linkage between the linker and hG-CSF occurs via a carbohydrate moiety on hG-CSF. This resultant structure is similar to the instantly claimed conjugate with the exception that Wright does not teach HAS/HES as the water-soluble starch polymer, and there is no disclosure as to what site on starch the carbohydrazide linker is conjugated at.

With regards to the missing element of HAS/HES, Berger *et al.* teach that HAS/HES is the polymeric drug carrier of choice because this polymer has the property of a low long term *in vivo* persistence, and can be metabolized, with little, if any, toxicity,

or excreted from the body, after it has served its function. Thus, the teachings of Berger *et al.* is sufficient to further narrow the prior art universe to a finite number of identified, predictable starch polymers.

The remaining missing element between the resultant conjugate based on the combined teachings of Wright, the Ishikawa '778 patent, Rotondaro *et al.*, and Berger *et al.*, is that the combined teachings of the thus far mentioned prior art does not teach or suggest the site of attachment of the carbohydrazide linker to starch. However, the Sommermeyer '909 patent discloses conjugation of haemoglobin to HES via the oxidized reducing end moiety, and Peluso *et al.* teach chemoselective ligation of hydrazide moieties to the reducing end, further teaching that chemoselective ligation is an attractive strategy as it allows the convergent synthesis of neoglycopeptides without the need for protecting groups or activating agents. Thus, in view of the teachings of the Sommermeyer '909 patent and Peluso *et al.*, one of ordinary skill in the art would have been motivated to conjugate the hydrazide linker to HAS/HES at its reducing end residue, with a reasonable expectation of success, since this reaction involves chemoselective ligation, thereby obviating the need for protecting groups or activating agents.

Applicants furthermore submit that the combined teachings of the cited references do not suggest a HAS-G-CSF conjugate as recited in the present claims. With regards to Wright, Applicants argue that Wright contains no teaching regarding functionalization of a polymer via groups other than hydroxyl groups or amino groups, and thus, a person starting from Wright would have had no reason to modify the

compounds taught by Wright so as to prepare a compound by coupling a linker selectively to the non-oxidized reducing end of a polysaccharide. With regards to the Sommermeyer '909 patent, Applicants argue that the Sommermeyer '909 patent does not teach or suggest any conjugate in which a HAS moiety is linked via an imine bond or an amine bond to a hydrazide linker compound, wherein the linker compound in turn is attached to the protein via an imine bond, These arguments have been fully considered but are not found persuasive because the Sommermeyer '909 patent discloses conjugation of HES to haemoglobin via the oxidized reducing end of HES, further teaching that conjugation at this site overcomes the prior art issues with respect to non-specific conjugation, which results in heterogeneous mixtures with different biological activities (column 3, lines 39-45; column 2, lines 47-49). Thus, one of ordinary skill in the art would have been motivated to conjugate a polypeptide to the reducing end residue of HES, rather than non-specifically to the numerous hydroxyl groups present on HES as suggested by Wright, in order to receive the expected benefit that conjugation on this residue would yield a specific conjugation reaction, thereby yielding a homogenous product with similar biological activities. Although the Sommermeyer '909 patent discloses conjugation to the reducing end residue of starch which has been oxidized, Peluso *et al.* teach that a chemoselective reaction can be achieved between a non-oxidized reducing sugar and hydrazine, thereby obviating the need for protecting groups. Thus, rather than conjugation to HES via the oxidized reducing end residue, one of ordinary skill in the art would have been motivated to conjugate HES via the non-oxidized reducing end residue, in order to receive the

expected benefit that the chemoselective reaction obviates the need for protecting groups. It is noted that Applicants argue that the reaction behavior of large molecules such as polysaccharides and polypeptides is significantly different from the reaction behavior of monosaccharides and small peptides, and therefore, any teaching regarding the synthesis of conjugates comprising monosaccharides and small oligopeptides cannot necessarily be transferred to large polysaccharides and polypeptides. Thus, Applicants submit that a skilled person starting with Wright and searching for advantageous new conjugates between polysaccharides and proteins would not have taken the teaching of Peluso into account.

Applicants' arguments have been carefully considered but are not persuasive. In view of the advantage disclosed by Peluso *et al.* that their disclosed chemoselective ligation method obviates the need for protecting groups, one of ordinary skill in the art would clearly consider such a method. Although Applicants argue that any teaching regarding the synthesis of conjugates comprising monosaccharides and small oligopeptides cannot necessarily be transferred to large polysaccharides and polypeptides, obviousness does not require absolute predictability, only a reasonable expectation of success, i.e., a reasonable expectation of obtaining similar properties. See, e.g., *In re O 'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988). See also MPEP § 2143.06(e). Since the structures are similar, one of ordinary skill in the art would have a reasonable expectation of success. Moreover, conjugation of a carbohydrazide moiety to the non-oxidized reducing end of HAS/HES eliminates an oxidation step, which one of ordinary skill in the art would consider advantageous as it

would requires less steps and less reagents. Thus, under the current legal standard for obviousness (*KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. at 398 (2007), 82 USPQ2d at 1396), since there is a finite number of compounds to try, namely, one chemoselective reaction, it would have been *prima facie* obvious for one of ordinary skill in the art to try making such a compound, with the expectation that it would result in the desired conjugate. The rationale to support a conclusion that the claim would have been obvious is that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely that product [was] not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. at 398 (2007), 82 USPQ2d at 1397. See also MPEP § 2143. Although Applicants also argue that even if such a skilled person would have taken Peluso *et al.* into account, they would not have arrived at the presently claimed conjugates because Peluso *et al.* do not teach or suggest a conjugate between a polysaccharide and a protein in which a bifunctional linking compound links both compounds. This argument is not persuasive because one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Moreover, one of ordinary skill in the art, having the cited references before him/her, would have used the Peluso *et al.* teachings to modify the combined disclosures of Wright, the

Ishikawa '778 patent, and the Sommermeyer '909 patent to arrive at the instantly claimed conjugate.

Applicants also argue that the Ishikawa '778 patent contains no suggestion that G-CSF should be coupled to PEG via a carbonyl group present in the glycoprotein, let alone any coupling via a carbonyl group using a bifunctional carbohydrazide linker or conjugation to the polysaccharide via the reducing end. As discussed above, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Moreover, the disclosures of Wright that it may be advantageous to couple water-soluble polymers to the carbohydrate moiety of a glycoprotein rather than to the polypeptide backbone amino acids because of differences in charge displacement, steric hinderance, amino acid residues at active sites, and other problems that may disrupt the structure and function of the polypeptide component of the water-soluble polymer modified glycoproteins, provides motivation for one of ordinary skill in the art to use the linker as disclosed in Wright for conjugation to the oxidized carbohydrate moiety of hG-CSF. Motivation for conjugation to the reducing end residue is disclosed in the Sommermeyer '909 patent, in teaching that conjugation to the hydroxyl groups are non-specific, leading to compositions of varying activity, which can be overcome by conjugation to the reducing end residue of HAS/HES.

The rejection is still deemed proper and therefore maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).
A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 56, 72, 73, 75 and 76 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 7, 8, 10 and 14 of copending application no. 11/518,558 (issued as U.S. Patent No. 8,017,739 on 13 September 2011), in view of U.S. Patent No. 5,824,778 to Ishikawa *et al.* (hereinafter referred to as the '778 patent; of record).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a method for preparing a conjugate comprising an oxidized protein and a hydroxyalkyl starch polymer derivative, the method comprising reacting at least one functional group A of the polymer derivative with at least one functional group Z of the oxidized protein, thereby forming a covalent linkage. The protein is selected from the group consisting of IFN beta, GM-CSF, APC, tPA, A1AT, ATIII, factor VII, factor VIII, and factor IX. A is an aldehyde group or a keto group. HAS is hydroxyethyl starch with a molecular weight

from 2 to 200 kD. The at least one bifunctional linking compound is a homobifunctional compound. A is an aminooxy group or a hydrazide group.

The claims of the instant application are drawn to a conjugate comprising a protein and a polymer, wherein the polymer is HAS and the protein is G-CSF, and the conjugate has the structure as recited in claim 56. HAS is HES with a molecular weight of from 2 to 200 kD.

The copending application does not expressly disclose G-CSF as a protein for conjugation. However, the Ishikawa '778 patent discloses conjugation of PEG to G-CSF to improve the half-life of the protein. Thus, it would have been *prima facie* obvious for one of ordinary skill in the art to substitute the PEG water-soluble polymer with the HES water-soluble polymer to arrive at the instantly claimed invention, since both water-soluble polymers are taught in the prior art to be useful for improving the solubilities and/or half-life of the protein they are conjugated to.

Thus, the instant claims 56, 72, 73, 75 and 76 are seen to be obvious over claims 1-3, 7, 8, 10 and 14 of copending application no. 11/518,558 (issued as U.S. Patent No. 8,017,739 on 13 September 2011), in view of U.S. Patent No. 5,824,778 to Ishikawa *et al.*

Applicants are requested to note that in view of the issuance of copending application no. 11/518,558 as U.S. Patent No. 8,017,739, this obviousness-type double patenting rejection is no longer provisional.

Claims 56, 72, 73, 75 and 76 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 60 and 61 of copending application no. 12/824,618, in view of EP 0605963 A2 to Wright (IDS dated 26 December 2006), in view of U.S. Patent No. 5,824,778 to Ishikawa *et al.* (hereinafter referred to as the '778 patent; of record).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a HAS derivative obtainable by a method comprising reacting a first HAS derivative obtained by reacting HAS of formula (I) at its optionally oxidized reducing end with a compound (D), said compound (D) comprising at least one functional group Z_1 capable of being reacted with the optionally oxidized reducing end of the HAS, and at least one functional group W. Functional group Z_1 and W is selected from the group that encompasses hydrazides. The copending application is also drawn to a composition comprising a therapeutically effective amount of HAS derivative.

The claims of the instant application are drawn to a conjugate comprising a protein and a polymer, wherein the polymer is HAS and the protein is G-CSF, and the conjugate has the structure as recited in claim 56. HAS is HES with a molecular weight of from 2 to 200 kD.

The copending application does not expressly disclose conjugation of HAS to G-CSF. However, Wright *et al.* teach conjugation of water-soluble polymers such as PEG or starch to a protein via hydrazide or hydroxylamine linkers to obtain increased desirable properties. Furthermore, the Ishikawa '778 patent discloses conjugation of

PEG to G-CSF to improve the half-life of the protein. Thus, it would have been *prima facie* obvious for one of ordinary skill in the art to conjugate the HAS derivative of the copending application to proteins, such as G-CSF to improve its solubility and/or half-life.

Thus, the instant claims 56, 72, 73, 75 and 76 are seen to be obvious over claims 60 and 61 of copending application no. 12/824,618, in view of EP 0605963 A2 to Wright, in view of U.S. Patent No. 5,824,778 to Ishikawa *et al*.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 56, 72, 73, 75 and 76 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, 9, 17-20, 27 and 29 of copending application no. 13/018,648, in view of U.S. Patent No. 5,824,778 to Ishikawa *et al*. (hereinafter referred to as the '778 patent; of record).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a conjugate comprising an oxidized protein and a hydroxyalkyl starch polymer. The protein is selected from the group consisting of IFN beta, GM-CSF, APC, tPA, A1AT, ATiii, factor VII, factor VIII, and factor IX. HAS is hydroxyethyl starch with a molecular weight from 2 to 200 kD. The conjugate has the structure as shown in claim 17. The copending application is also drawn to compositions comprising the conjugate.

The claims of the instant application are drawn to a conjugate comprising a protein and a polymer, wherein the polymer is HAS and the protein is G-CSF, and the conjugate has the structure as recited in claim 56. HAS is HES with a molecular weight of from 2 to 200 kD.

The copending application does not expressly disclose G-CSF as a protein for conjugation. However, the Ishikawa '778 patent discloses conjugation of PEG to G-CSF to improve the half-life of the protein. Thus, it would have been *prima facie* obvious for one of ordinary skill in the art to substitute the PEG water-soluble polymer with the HES water-soluble polymer to arrive at the instantly claimed invention, since both water-soluble polymers are taught in the prior art to be useful for improving the solubilities and/or half-life of the protein they are conjugated to.

Thus, the instant claims 56, 72, 73, 75 and 76 are seen to be obvious over claims 1-6, 9, 17-20, 27 and 29 of copending application no. 13/018,648, in view of U.S. Patent No. 5,824,778 to Ishikawa *et al.*

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

Applicants' intent that the obviousness-type double-patenting rejections above be held in abeyance until the present claims are otherwise found to be allowable, at which point Applicant will file a terminal disclaimer over the various applications, in the reply filed on 21 September 2011, is acknowledged.

The rejections are still deemed proper, and are therefore maintained.

Conclusion

In view of the rejections to the pending claims set forth above, no claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SCARLETT GOON whose telephone number is (571)270-5241. The examiner can normally be reached on Mon - Thu 7:00 am - 4 pm and every other Fri 7:00 am - 12 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SCARLETT GOON/
Primary Examiner, Art Unit 1623